Clinical Neurophysiology 154 (2023) 49–59

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

The influence of very preterm birth on adolescent EEG connectivity, network organization and long-term outcome

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HIGHLIGHTS

- Very preterm born adolescents may have altered functional connectivity and brain network topology that is specific to the beta frequency band.
- Connectivity and network measures in the beta frequency band were associated with functioning.
- Alterations in brain activity measures did not mediate the relation between prematurity and long-term outcomes.

ARTICLE INFO

Article history:
Accepted 13 July 2023
Available online

Keywords:
Prematurity
Functional connectivity
Network analysis
Long-term outcome

ABSTRACT

Objective: The aim of this study was to explore differences in functional connectivity and network organization between very preterm born adolescents and term born controls and to investigate if these differences might explain the relation between preterm birth and adverse long-term outcome.
Methods: Forty-seven very preterm born adolescents (53% males) and 54 controls (54% males) with matching age, sex and parental educational levels underwent high-density electroencephalography (EEG) at 13 years of age. Long-term outcome was assessed by Intelligence Quotient (IQ), motor, attentional functioning and academic performance. Two minutes of EEG data were analysed within delta, theta, lower alpha, upper alpha and beta frequency bands. Within each frequency band, connectivity was assessed using the Phase Lag Index (PLI) and Amplitude Envelope Correlation, corrected for volume conduction (AEC-c). Brain networks were constructed using the minimum spanning tree method.
Results: Very preterm born adolescents had stronger beta PLI connectivity and less differentiated network organization. Beta AEC-c and differentiation of AEC-c based networks were negatively associated with long-term outcomes. EEG measures did not mediate the relation between preterm birth and outcomes.
Conclusions: This study shows that very preterm born adolescents may have altered functional connectivity and brain network organization in the beta frequency band. Alterations in measures of functional connectivity and network topologies, especially its differentiating characteristics, were associated with neurodevelopmental functioning.
Significance: The findings indicate that EEG connectivity and network analysis is a promising tool for investigating underlying mechanisms of impaired functioning.

1. Introduction

Very preterm birth (<32 weeks' gestation) substantially increases the risk of adverse long-term outcome in multiple neurodevelopmental domains, including cognition, motor

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https://doi.org/10.1016/j.clinph.2023.07.004
1388-2457/

performance, behavior and academic performance (Luu et al., 2017). Many risk factors for adverse neurodevelopmental outcome have been identified, such as intraventricular hemorrhage and periventricular leukomalacia (Keunen et al., 2012). However, there is an increased awareness that infants without major structural lesions or abnormalities are susceptible to adverse neurodevelopment as well (de Vries et al., 2015). For example, a number of imaging studies has associated adverse long-term outcome with diffuse white matter atrophy, lower white matter integrity and smaller (sub)cortical grey matter volumes (Counsell and Boardman, 2005, de Kieviet et al., 2012, Woodward et al., 2012). These structural cerebral abnormalities, however, only explain a small part of the heterogeneity in long-term outcome of the very preterm born population (Jansen et al., 2021, Van't Hooft et al., 2015). The underpinnings of adverse neurodevelopmental outcome remain poorly understood. Therefore in addition to brain structure, more insight into atypical brain function after very preterm born birth is of interest.

One of the techniques to assess brain function is quantitative electroencephalography (EEG) analysis, which includes functional connectivity and network analysis. Evidence suggests that brain functions, such as intelligence, greatly depend on efficient spatially remote neural synchronization, i.e. functional connectivity, which can be thought of as communication between brain regions (Neubauer and Fink, 2009). This communication is organized in multiple brain networks that function on different time scales (Siegel et al., 2012). The characteristics of brain networks can be studied by network measures that give insight into how they are organized (Bullmore and Sporns, 2009). Previous evidence, based on EEG data of ~400 adolescents, showed that during adolescence, the brain matures with increasing functional connectivity, as measured by the synchronization likelihood, and clustering within functional networks (Smit et al., 2012). Furthermore, abnormal functional connectivity and network organizations have been shown to be key features in a wide range of disorders, including attention deficit/hyperactivity disorder, autism spectrum disorder and dyslexia (Bailey et al., 2018, Rudie et al., 2012, Sutcubasi et al., 2020), and differences in EEG functional connectivity between very preterm and term born infants have been observed (Gonzalez-Moreira et al., 2021, González et al., 2011).

Several EEG paradigms exist, including analysis of data derived during resting state or task performance. Many attempts have been made to identify EEG correlates of cognition, including local cortical activation patterns linked to task performance. However, there is a large body of evidence that suggests that ongoing spontaneous neural activity during resting state is spatiotemporally organized in so-called resting-state networks, and that these are critical for complex goal-directed behavior in addition to task-induced dynamics (Dubois et al., 2018, Park and Friston, 2013, Van Den Heuvel and Pol, 2010). For example, the Parieto-Frontal Integration Theory of intelligence states that intelligence is not focal, but emergent from the resting-state parietal-frontal network (Jung and Haier, 2007, Langer et al., 2012). It is assumed that cognitive functioning is related to global properties, i.e. organization within brain networks, as well as local properties, i.e. sole activation of cortical regions, of neural processing (Stam and van Straaten, 2012). Therefore, studying correlates of resting-state EEG connectivity and network organization and long-term outcomes may give us insight into how differences in outcome measures between very preterm and term born individuals may be explained.

Previous neurophysiology research suggests that neurophysiological functional connectivity measures, in particular phase locking values in the alpha frequency band, might add to the explanation of the heterogeneity in task performance in very preterm born individuals at 7–8 years of age (Doesburg et al., 2011, Moiseev et al., 2015). The Phase Lag Index (PLI) is a functional connectivity measure, more specifically a phase coupling measure, that indicates the consistency with which one EEG signal is phase leading or lagging another signal. Another functional connectivity measure is the Amplitude Envelope Correlation (AEC). The AEC gives insight into the coupling between fluctuations in EEG amplitudes of two signals, thereby reflecting slightly slower functional synchronization, and has a close relation with structural and functional magnetic resonance imaging (fMRI) connectivity (Engel et al., 2013). It is thought that PLI and AEC may complement each other in functional connectivity research (Siems and Siegel, 2020; Mostame P., Sadaghiani S).

fMRI studies have shown altered connectivity patterns in large-scale resting state brain networks, including the prominent default mode network (DMN) (Raichle et al., 2001), of very preterm born children and adolescents, and these alterations were associated with neurodevelopmental impairments (Daamen et al., 2015, Wehrle et al., 2018, Wheelock et al., 2018, White et al., 2014). Brookes and colleagues suggested selection of the AEC as functional connectivity measure in magnetoencephalography (MEG) studies, since AEC networks in alpha and beta frequency bands showed similar compositions as those derived from resting-state fMRI in healthy adults (Brookes et al., 2011). EEG has similar temporal resolution as compared to MEG, making it an appropriate tool for investigating differences in functional connectivity and brain networks, and since it is a relatively easy method to apply, it is more suitable for obtaining information on brain activity in adolescents than more burdensome neuroimaging techniques such as fMRI. Previous EEG studies showed that alpha and beta oscillations are related to resting-state networks that share overlap with the DMN and attentional networks (Mantini et al., 2007), and intracranial EEG connectivity analyses showed slow-wave intra-DMN connectivity and fast-wave (beta and gamma) connectivity between the DMN and other brain regions (Das et al., 2022, Hacker et al., 2017). Currently, little is known about long-term very preterm birth-related alterations in global EEG functional connectivity and network organizations.

The aim of this study was therefore to examine EEG-based functional connectivity and network organization in very preterm and full-term born adolescents and to explore whether alterations in functional connectivity and network measures mediate the observed relation between very preterm birth and long-term neurodevelopmental impairments in adolescence. We hypothesized that differences in brain activity exist between very preterm born adolescents and controls, and that stronger connectivity and more differentiated networks are associated with better long-term outcomes. Based on earlier research that showed associations between brain activity and outcome measures, we additionally hypothesized that brain activity mediates the observed relation between very preterm birth and long-term outcomes.

2. Methods

2.1. Participants

Between 2001 and 2003, 102 very preterm born infants (gestational age (GA) < 32 weeks), admitted to the level three neonatal intensive care unit of the VU Medical Center, now the Amsterdam UMC, participated in a randomized controlled trial on enteral glutamine supplementation during the neonatal period. Exclusion criteria were major congenital or chromosomal anomalies, death <48 h after birth, transfer to another hospital <48 h after birth and admission from an extra-regional hospital (van den Berg et al., 2004). Detailed information on the intervention and the results of the trial are described in previously published studies (van den Berg et al., 2005, Van Zwol et al., 2008). There was no evidence for beneficial or adverse effects of enteral glutamine supplementation on long-term outcome, including motor performance, neurocognitive functioning, academic performance, behavior or absolute and relative EEG frequency band power (delta, theta, alpha, beta) at 13 years of age (Twilhaar et al., 2018, Twilhaar et al., 2019).

Eighty-eight very preterm born infants were alive at one year of age and eligible for follow-up. Sixty-one controls, matched in terms of age, sex and parental educational level to the sample of very preterm born adolescents, were recruited from the same school attended by the very preterm born adolescents, or other schools in the same area. Controls were born at term ($GA \geq 37$ weeks) and were free of neurologic or developmental disorders. Data collection took place between September 2015 and July 2016.

This study was conducted according to the Declaration of Helsinki and approved by the local ethical committee. Informed consent was obtained from both parents and participants.

2.2. EEG acquisition and post-processing

As previously described, resting-state EEGs were recorded at a sampling rate of 2048 Hz using the BioSemi Active Two system (BioSemi, Amsterdam, the Netherlands) (Twilhaar et al., 2019). Participants were sitting with their eyes closed for five minutes during a state of relaxed wakefulness. Sixty-four electrodes were attached to the scalp according to the International 10–20 system. Reference electrodes were placed at the mastoids. Brain Vision Analyzer software (Brain Vision Analyzer 2.1, Brain Products, Munich, Germany) was used to downsample the data to 512 Hz and to reference electrodes to the average reference. The bandpass lower and upper cutoffs were 0.1 Hz and 70 Hz, respectively. EEG data was converted to ASCII-format.

The BrainWave software (version 0.9.156.12, freely available from https://home.kpn.nl/stam7883/brainwave.html) was used for EEG connectivity and network analysis, including functional connectivity and network analysis. The epoch length was 4096 samples, i.e. 8 seconds (Fraschini et al., 2016), and epochs were visually assessed on substantial amounts of unwanted non-brain signals such as muscle artifacts and eye movements by one of the authors (CvtW). Per subject, 15 epochs that were artifact-free or had tolerable artifacts were selected (Fraschini et al., 2016). EEG recordings were filtered offline into five frequency bands using the Fast Fourier Transform: delta: 0.5–4 Hz; theta: 4–8 Hz; lower alpha: 8–10 Hz; upper alpha: 10–13 Hz; and beta: 13–30 Hz. In addition, median frequencies were calculated per epoch using the BrainWave software. The median frequency is calculated as the frequency between 4 and 13 Hz at which the median of the power values occurs, averaged over 64 channels and 15 epochs.

2.3. Functional connectivity analysis

Connectivity was assessed by two connectivity measures, namely the AEC corrected version (AEC-c) and PLI. Amplitude envelopes and phase differences can be calculated by using the Hilbert transformation to estimate instantaneous amplitudes and phases over time-series. Pair-wise orthogonalization is used to correct for volume conduction (Hipp et al., 2012), and the AEC is calculated as the Pearson's correlation between the amplitude envelopes of two time-series using the following equation (Bruns et al., 2000, Briels et al., 2020):

$$AEC = corr\,(h_x(t), h_y(t))$$

where $h_X(t)$ and $h_Y(t)$ are the envelopes of time-series X and Y, respectively, *corr* is the Pearson's correlation coefficient. The BrainWave software subsequently uses the following formula to transform the AEC values to a range from 0 to 1;

$$AEC - c = \frac{(AEC + 1)}{2}$$

in which 0 reflects a correlation of -1, 0.5 a correlation of 0 and 1 a correlation of 1.

The PLI discards phase differences that centre around zero modulo pi and thereby diminishes the influence of volume conduction on the functional connectivity analysis, since non-zero phase lags cannot be explained by common sources of brain activity (Stam et al., 2007). The PLI is calculated using the following equation:

$$PLI = |\langle[\mathrm{sign}(\Delta\varphi(t_k))]\rangle|$$

where $\Delta\varphi(t_k)$ is the phase difference, calculated for time point t_k with k = 1...N, dependent on the sampling frequency. *Sign* refers to the signum function, which translates a positive value for the phase difference into 1, a negative value for the phase difference into -1 and no phase difference into 0. < > refers to the mean value and || denotes absolute values.

AEC-c and PLI values were computed per frequency band and epoch and results were averaged across all pairwise channels for each matrix. The mean AEC-c or PLI was calculated as the average over 15 epochs per subject.

2.4. Functional network analysis

In functional network science, graphs are used as mathematical representations of functional connectivity networks and consist of nodes representing electrodes and links representing functional connectivity strengths between the nodes they connect. The minimum spanning tree method constructs networks by using the Kruskal algorithm, which connects all nodes that show the strongest connectivity without forming loops, resulting in a so-called 'tree' that can be seen as the backbone of the network (Stam et al., 2014). Consequently, minimum spanning tree networks have a fixed number of connections and nodes, which makes it an unbiased method to compare minimum spanning tree networks between groups than conventional networks, i.e. graphs that only include links when the associated connectivity value exceeds a set threshold (Stam et al., 2014, Tewarie et al., 2015). The method was applied per connectivity matrix and thus per frequency band and epoch. Resulting trees consisted of 64 nodes and 63 connections.

Network measures that were used to gain insight in network organization across the five frequency bands included maximum degree (maxDEG), leaf fraction (LF), tree hierarchy (TH) and maximum betweenness centrality (maxBC) (Stam et al., 2014). The measures maxDEG, LF, TH and maxBC were calculated per minimum spanning tree, with maxDEG being the fraction of connections of the best-connected node in the network. For example, in a network with 63 connections in which the best-connected node has 21 connections, maxDEG = 21/63 = 0.33. LF was calculated as the fraction of nodes that had exactly-one connection, and maxBC was calculated as the fraction of paths that pass through the node with the highest passing load. TH is a measure that integrates criteria for an optimal network organization, i.e. an intermediate state with an optimal balance between segregation and integration (Fig. 1) (Boersma et al., 2013). TH reflects the balance between a high number of 'leafs' and an overloaded hub, i.e. a node with a high number of paths passing through. TH has the following formula:

$$TH = \frac{l}{2 * m * maxBC}$$

where *l* is the number of leafs, *m* is the number of connections and *maxBC* is the fraction of paths that pass through the node with the

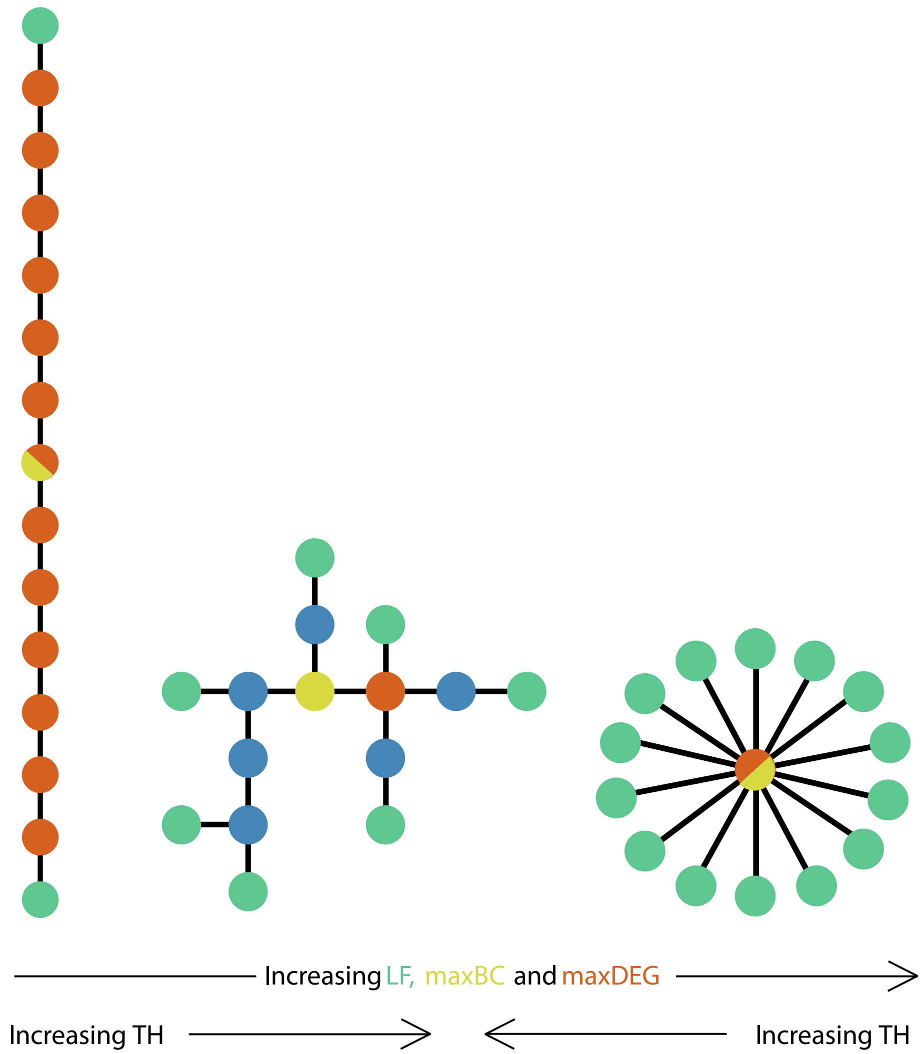

Fig. 1. Three tree examples and the increasing direction for the network measures LF, maxDEG, maxBC and TH. Circles are nodes (n = 15) and lines are links (n = 14). The left tree is the extreme line-like topology and the right tree is the extreme star-like topology. TH is a function of the leaf number, the amount of connections (i.e. n = 14) and maxBC. maxDEG = maximum degree; LF = leaf number; maxBC = maximum betweenness centrality; TH = tree hierarchy.

highest passing load. The more the network approaches a line-like topology, i.e. having less leafs, the lower the TH outcome will be. On the contrary, when there is a star-like topology with $m = l$ and maxBC = 1, the TH outcome will be 0.5. Every other topology between star-like and line-like topologies will result in a TH value higher than 0.5 (Boersma et al., 2013). Fig. 1 shows how network measures can reflect network topologies by providing several minimum spanning tree examples. Network measures were calculated in both PLI and AEC-c constructed minimum spanning tree networks and were averaged across the 15 epochs per subject.

2.5. Cognitive, motor, behavioral and academic measures

Neurodevelopmental outcomes were assessed as previously described (Twilhaar et al., 2018). Intelligence was assessed using a short form of the Wechsler Intelligence Scale for Children 3th Ed., Dutch version (WISC-III-NL) (Wechsler, 1992). Full-scale Intelligence Quotient (IQ) scores were estimated based on the Vocabulary and Block Design subtests. This short form of the WISC-III-NL has a high reliability (r = 0.91) and shows a strong correlation (r > 0.90) with full-scale IQ (Sattler, 2018).

Motor function was assessed with the Dutch version of the Movement Assessment Battery for Children, second edition (MABC-2-NL) (Henderson et al., 2007). The MABC-2-NL comprises eight tasks to measure manual dexterity, ball skills, and static and dynamic balance. Raw total scores were used for the analyses.

The parent- and teacher-rated Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN) questionnaire was used to assess inattention (Swanson et al., 2012). Attentional performance was rated on a 7-point Likert scale, ranging from −3 (far below average) to +3 (far above average), anchored to average behavior. Raw total scores were used for the analyses.

Academic performance was assessed using standardized tests developed by the Dutch National Institute for Educational Measurement (Gillijns and Verhoeven, 1992). Standardized tests regarding reading comprehension, spelling and arithmetic performance are part of a national monitoring system to assess children's academic progression during primary school (age range 4–12 years). Data were requested from schools after informed consent of both participants and parents. The most recent test scores were used per participant (at approximately 12 years of age).

2.6. Statistical analysis

Data analyses were performed using R statistical software version 3.1.1 (Team, 2013) and SPSS version 23.0 (IBM Corp. Released

2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.). EEG connectivity and network measures were transformed with the Van der Waerden transformation using the R package bestNormalize to correct for the skewness in the data distributions and outliers, defined as the absolute value of datapoints that are above three times the interquartile range (Lehmann and D'Abrera, 1975, Peterson and Cavanaugh, 2019). For the comparisons between very preterm born adolescents and controls, cohen's *d* was used to quantify effect sizes for the independent samples *t*-tests (0.2 = small, 0.5 = medium and 0.8 = large effect) and linear mixed-effects model analyses were performed including very preterm birth and median frequencies as fixed effects and random slopes for family clusters to take into account dependencies between observations from twins and triplets. The Benjamini-Hochberg procedure was applied to correct for multiple comparisons per frequency band ($p < 0.05$, corrected, $q = 0.05$).

In the frequency band that showed significant group differences, associations were quantified between sex and age during follow-up and EEG connectivity and network measures by calculating independent samples *t*-tests and Pearson's correlation coefficients. Within the very preterm born group, independent samples *t*-tests were calculated for glutamine supplementation (yes/no) and the same EEG connectivity and network measures to investigate the effect of glutamine on the quantitative EEG measures.

Mediation analyses were performed using the R package lavaan to investigate if the associations between very preterm birth and long-term outcome were mediated by functional connectivity and network organization in the frequency band that showed significant group differences. Parallel multiple mediator models that simultaneously test the role of all EEG connectivity and network measures were constructed to account for the interrelatedness of these measures (Fig. 2) (Hayes, 2013, MacKinnon, 2008). Determinant-mediator interaction effects, i.e. the interaction effect of very preterm birth on the relation between EEG connectivity and network measures and long-term outcomes, were exploratively investigated for all mediators in the constructed models ($n = 60$) to investigate if the mediator (i.e. the quantitative EEG measures) behaves differently dependent on the value of the determinant (i.e. very preterm birth). 95% confidence intervals were estimated for the path regression coefficients and indirect effects using 1000 bootstrap resamples and the bootstrap-based *p*-values were reported. Wald statistics, i.e. the regression coefficients divided by their standard errors, were calculated. If a Wald statistic has a magnitude larger than 1.96, then the regression coefficient is statistically significant at the 95% level. The Wald statistics are reported as absolute z-values for the significant associations to give insight into effect sizes.

Significance levels were set at a *p*-value of less than 0.05.

3. Results

3.1. Sample characteristics

Fifty-five preterm born individuals participated at 13 years of age in the present study. Two adolescents were unable to complete the EEG recording due to disability and behavioral difficulties. Forty-seven of 53 very preterm born adolescents and 54 of 61 age-matched controls had an EEG of sufficient quality for selection of 15 epochs for quantitative EEG analysis. Compared to the adolescents included in the study analyses ($n = 47$), adolescents not included in the study analyses ($n = 41$) had higher rates of intraventricular hemorrhages grades I or II (Fisher's exact test, $p = 0.046$) and lower birth weight ($t(86) = -3.30$, $p = 0.001$, mean difference = 233 grams) (Appendix A, Table A.1). Furthermore, the 13 adolescents with insufficient data quality had significantly lower full-scale IQ, MABC-2-NL, and arithmetic, reading comprehension and spelling scores compared to those with sufficient data quality (see Appendix A, Table A.2). The sample characteristics of the study and control groups are shown in Table 1. Very preterm born adolescents and controls did not differ regarding sex, age at follow-up and parental educational levels.

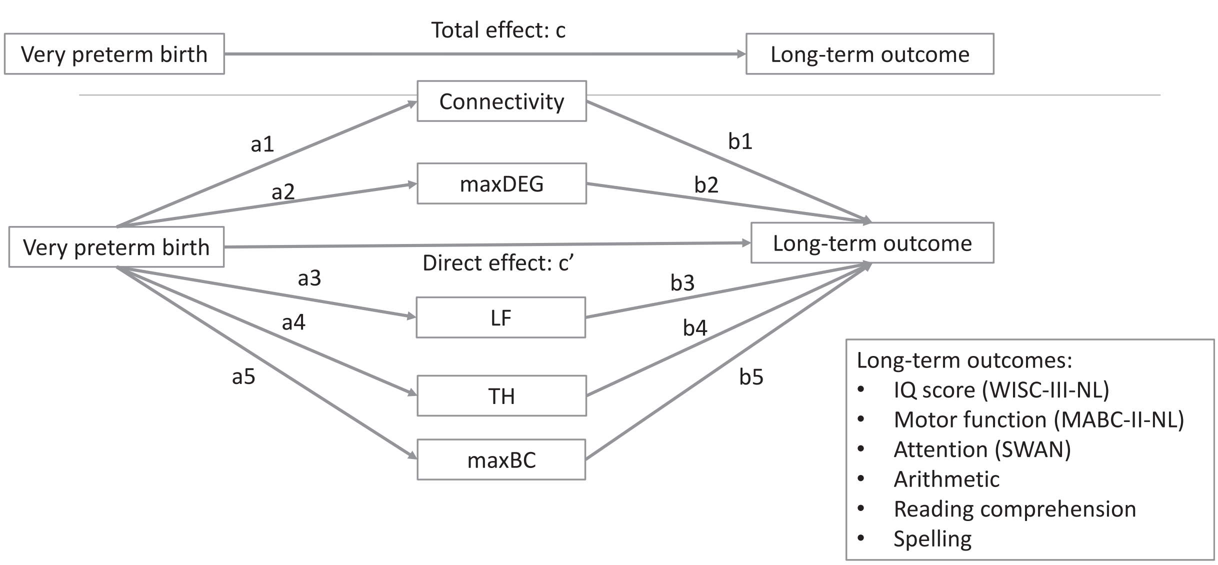

Fig. 2. Graphical representation of the parallel multiple mediator model. c paths reflect the total effect of very preterm birth on the outcome measure, a paths reflect the effect of very preterm birth on quantitative EEG measures, b paths reflect the effect of EEG connectivity and network measures on long-term outcome controlled for the effect of very preterm birth, and c' paths reflect the direct effect of very preterm birth on outcome, controlled for the potential mediating effects of the quantitative EEG measures. Indirect effects (mediation effects) reflect the effect of very preterm birth on an outcome measure through a certain mediator (in this case, quantitative EEG measures) controlling for the other mediators in the parallel model. Indirect effects are calculated as the product of coefficients a and b per mediator. The total effect c equals the sum of the direct and indirect effects. maxDEG = maximum degree; LF = leaf number; maxBC = maximum betweenness centrality; TH = tree hierarchy; IQ = Intelligence Quotient; WISC-III-NL = Wechsler Intelligence Scale for Children 3th Ed., Dutch version; MABC-2-NL = Movement Assessment Battery for Children, second edition, Dutch version; SWAN = Strengths and Weaknesses of ADHD Symptoms and Normal Behavior.

Table 1
Sample characteristics.

	Very preterm (*n* = 47)	Full-term (*n* = 54)	*P*-value
Sex, *n* (%) boys	25 (53)	29 (54)	0.559
Age, years, M (SD)	13.29 (0.29)	13.22 (0.54)	0.398
Parental education, *n* (%) ≥bachelor degree or equivalent	28 (60)	35 (65)	0.368
Perinatal risk factors[a]			
GA, weeks, M (SD)	29.34 (1.53)		
BW, grams, M (SD)	1295.83 (350.94)		
SGA, *n* (%)	9 (19)		
Caesarean section, *n* (%)	26 (55)		
BPD, *n* (%)	11 (23)		
IVH grade I/II, *n* (%)	7 (15)		
IVH grade III/IV, *n* (%)	0 (0)		
PVL, *n* (%)	1 (2)		
PDA, *n* (%)	6 (13)		
ROP, *n* (%)	2 (4)		
NEC, *n* (%)	0 (0)		
≥1 serious neonatal infection, *n* (%)[b]	29 (62)		
Long-term outcome			
IQ (WISC-III-NL full-scale IQ scores), mean (SD)	99.30 (16.21)	111.09 (10.76)	<0.001
Motor function (MABC-2-NL total scores), mean (SD)	67.57 (17.50)	78.93 (10.11)	<0.001
Attention (parent- and teacher-rated SWAN attention scores), mean (SD)	0.06 (0.91)	0.62 (0.77)	0.001
Arithmetic, mean (SD)	109.29 (15.78)	119.08 (11.30)	0.001
Reading comprehension, mean (SD)	58.40 (20.13)	68.06 (18.43)	0.016
Spelling, mean (SD)	145.02 (7.55)	148.0 (8.83)	0.081

[a] Perinatal risk factors included GA, birth weight, retinopathy of prematurity (as classified by the The Committee for the Classification of Retinopathy of Prematurity (1984)), intraventricular hemorrhage (as classified by (Papile et al., 1978)), patent ductus arteriosus (treated with indomethacin or surgical ligation), bronchopulmonary dysplasia (as classified by Jobe and Bancalari, 2001) and infections (defined as sepsis, pneumonia, meningitis, pyelonephritis or arthritis, as confirmed by a positive culture).
[b] Sepsis, pneumonia, meningitis, pyelonephritis, or arthritis diagnosed based on a combination of clinical signs and positive culture. M = mean; SD = standard deviation; GA = gestational age; BW = birth weight; SGA = small for gestational age; BPD = bronchopulmonary dysplasia; IVH = intraventricular hemorrhage; PVL = periventricular leukomalacia; PDA = patent ductus arteriosus; ROP = retinopathy of prematurity; NEC = necrotizing enterocolitis; IQ = Intelligence Quotient; WISC-III-NL = Wechsler Intelligence Scale for Children 3th Ed., Dutch version; MABC-2-NL = Movement Assessment Battery for Children, second edition, Dutch version; SWAN = Strengths and Weaknesses of ADHD Symptoms and Normal Behavior.

3.2. Group differences

Median frequencies were not significantly different between very preterm born adolescents and controls (t(98.06) = 0.39, p = 0.700, mean difference = 0.11 Hz, Appendix A, Fig. A.1). Fig. 3 shows the results of group comparisons between very preterm born adolescents and matched controls for EEG connectivity, averaged across all connections, and network measures in all frequency bands. Very preterm born adolescents had significantly stronger PLI connectivity in the beta frequency band, indicating altered global fast synchronization patterns (Fig. 4A–B). In addition, measures of network organization were significantly different, with stronger PLI maxDEG and LF and stronger AEC-c maxDEG and LF measures in the beta frequency band in very preterm born adolescents, pointing towards less differentiated network organization in very preterm born adolescents (Fig. 4C–D). The sizes of these effects were medium (Fig. 3). In Appendix A, Fig. A.2, plots of the group comparisons are displayed showing all data points of transformed and untransformed data for the PLI and AEC-c connectivity and network measures in all frequency bands. Mixed effect models showed that very preterm birth remained a significant predictor of PLI connectivity, maxDEG and LF and AEC-c maxDEG and LF after correcting for median frequencies and family clusters. median frequency was also a significant predictor for PLI connectivity, maxDEG and LF, whereas it was not for AEC-c maxDEG and LF (data not shown).

EEG connectivity and network measures in the beta frequency band were not correlated with sex, neonatal glutamine supplementation, and age at assessment.

3.3. Parallel multiple mediator models

Very preterm birth was associated with lower full-scale IQ scores, MABC-2-NL total scores, parent- and teacher-rated SWAN attention scores, arithmetic and reading comprehension (total effects, Appendix A, Fig. A.3 and Table A.3). There were no significant interactions of very preterm birth and EEG connectivity and network measures on long-term outcomes, meaning that the associations between EEG measures and outcomes did not differ according to preterm birth status.

When accounting for very preterm birth, beta connectivity measured with the AEC-c but not the PLI was negatively associated with parent- and teacher-rated SWAN attention scores (b = −0.27, z = 2.38), arithmetic (b = −4.67, z = 3.30), reading comprehension (b = −6.67, z = 3.94) and spelling (b = −2.06, z = 2.30) (b paths, Appendix A, Fig. A.3F–H–J–L and Table A.3). Table 2 shows an overview of the significant associations within the beta frequency band based on AEC-c calculations. AEC-c based LF was positively and AEC-c based TH and maxBC were negatively associated with arithmetic, reading comprehension, and full-scale IQ scores (TH only) in the beta frequency band, indicating that network differentiation may be negatively associated with long-term outcome after correction for very preterm birth (b paths, Appendix A, Fig. A.3B–H–J and Table A.3). However, the associations between very preterm birth and long-term outcome were not mediated by quantitative EEG measures, as indicated by the non-significant indirect effects (Appendix A, Fig. A.3 and Table A.3). Furthermore, direct effects show that very preterm birth remained significantly associated with long-term outcome measures independent of the quantitative EEG measures.

4. Discussion

The present study is one of the first to show alterations in measures of neurophysiological functional connectivity and network organization in adolescents born very preterm. More specifically, very preterm born adolescents had stronger PLI connectivity and

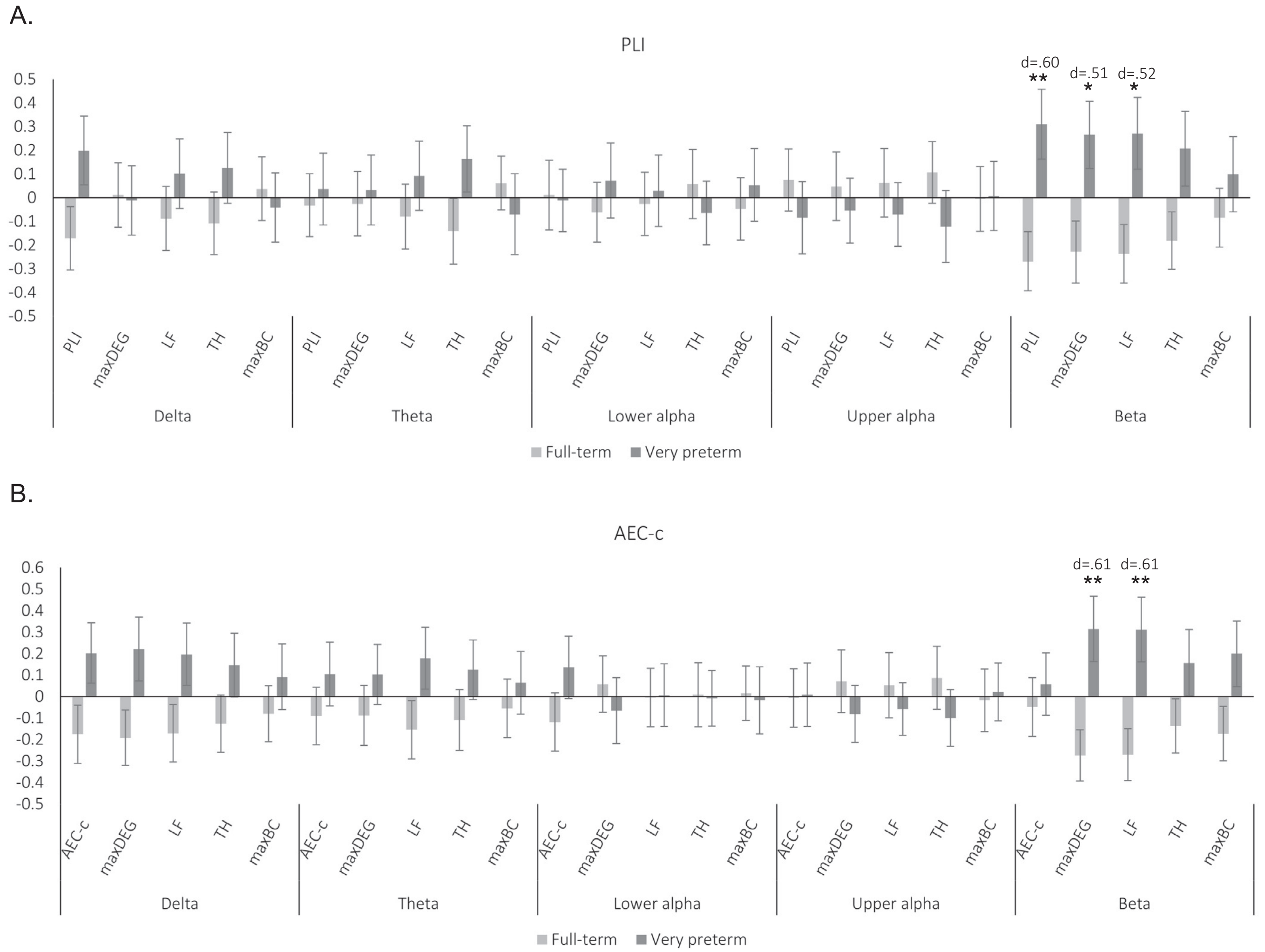

Fig. 3. Group comparisons between very preterm born adolescents ($n = 47$) and age-matched full-term born controls ($n = 51$) for quantitative EEG analysis results in the delta, theta, lower alpha, upper alpha and beta frequency bands based on PLI (A) and AEC-c (B) connectivity and network measures after correcting for median frequencies and family dependencies in linear mixed-effects models. *$p < 0.05$, **$p < 0.01$, significant after Benjamini-Hochberg multiple comparison correction. D = 0.2 'small' effect size, d = 0.5 'medium' effect size and d = 0.8 a 'large' effect size. PLI = Phase Lag Index; AEC-c = Amplitude Envelope Correlation – corrected version; maxDEG = maximum degree; LF = leaf fraction; TH = tree hierarchy; maxBC = maximum betweenness centrality.

a less differentiated network organization in the beta frequency band. AEC-c connectivity and network organization in the beta frequency band was associated with intelligence, academic performance, and attention. However, these neurophysiological characteristics did not explain the differences in outcomes between very preterm and full-term adolescents.

Previous studies, including one of our study group, provided evidence that very preterm born adolescents have lower spectral relative beta power compared to controls, whereas relative power of other frequency bands were not significantly different (Nunes et al., 2020; Twilhaar et al., 2019). This study additionally shows stronger PLI connectivity in the beta frequency band in very preterm born adolescents. It remains unclear if spectral power and functional connectivity within the same frequency band are coupled (Tewarie et al., 2019). Our findings support the idea that spectral power and functional connectivity are at least partly independent entities, since their associations with very preterm birth are in opposite directions, a phenomenon that also has been observed in the alpha frequency band in a study that longitudinally compared frequency power and synchronization likelihood connectivity in children at 5 and 7 years of age (Boersma et al., 2011). An explanation for this counterintuitive relation might be that there is an interplay between less efficient local neuronal synchronization and functional connectivity and network development that contribute to persisting alterations in brain development after preterm birth.

The increased beta functional connectivity in very preterm born adolescents is consistent with the findings of Barnes-Davis et al. who showed increased MEG beta functional connectivity, as measured with the weighted PLI, in extremely preterm born children compared to controls at 4–6 years of age (Barnes-Davis et al., 2018). In typically developing children, Smit et al. showed increasing EEG-based functional connectivity, as measured with the synchronization likelihood, in the alpha and beta frequency bands from childhood to adolescence (Smit et al., 2012), suggesting that stronger connectivity reflects more mature brain activity. The stronger functional connectivity in very preterm born adolescents in the present study, however, contrasts evidence of brain maturation delays through to childhood after very preterm birth (Vandewouw et al., 2020). On the other hand, our findings support a hypothesis that was recently postulated by Karolis and colleagues; based on their findings in grey matter structures, they created a "maturation index" and showed that preterm born individuals have higher indices than age-matched controls at

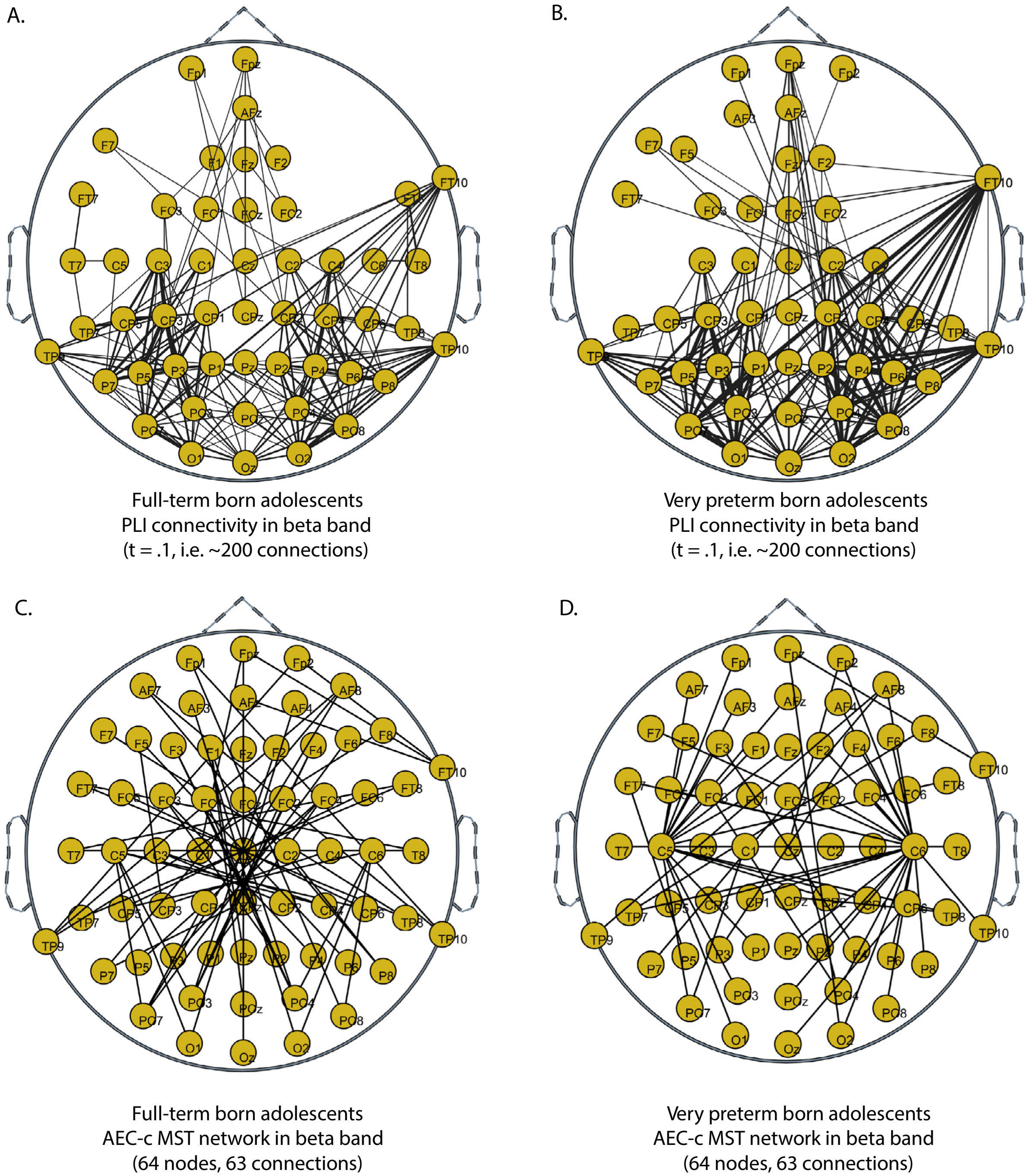

Fig. 4. Group-averaged PLI connectivity results per pairwise comparison with the 10% strongest connections shown (A and B) and AEC-c based MST networks (C and D) in the beta frequency band, projected on the scalp for the very preterm born adolescents (n = 47) (B and D) and age-matched full-term born controls (n = 51) (A and C). Thickness of the lines corresponds with the magnitude of the PLI value. PLI = Phase Lag Index; AEC-c = Amplitude Envelope Correlation – corrected version; MST = Minimum Spanning Tree; t = threshold.

~15, ~20 and ~30 years of age. These findings parallel the stronger connectivity in very preterm born adolescents observed in the present study. They hypothesized that very preterm birth-related white matter abnormalities might mimic ageing processes in the brain that subsequently accelerate rather than delay brain maturation from the time of adolescence (Karolis et al., 2017). Furthermore, the current study provided evidence for less differentiated network organization in very preterm born adolescents as compared to full-term born controls, since they showed higher maxDEG and LF in PLI as well as AEC-c based networks in the beta frequency band. These findings suggest that an altered prematurity-specific network organization exists. These alterations may be a result of altered brain maturation speed or compensatory mechanisms that affect neurodevelopment due to complex damage and repair mechanisms that occur in the brain after very preterm birth (Shaw et al., 2021).

Another explanation for the observed differences in brain activity between very preterm born adolescents and controls may be

Table 2
Overview of associations between long-term outcomes and measures based on AEC-c connectivity and network calculations. Separate mediation models were tested for full-scale IQ scores of the WISC-III-NL, motor function as measured by the MABC-2-NL total scores, attention as measured by the parent- and teacher-rated SWAN attention scores and academic performances of arithmetic, reading comprehension and spelling. Significant estimated effects of quantitative EEG measures on long-term outcome are indicated with *$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$. b-values and z-values (parentheses) are shown. IQ = intelligence quotient; maxDEG = maximum degree; LF = leaf number; TH = tree hierarchy; maxBC = maximum betweenness centrality.

	Connectivity	maxDEG	LF	TH	maxBC
IQ	−2.0 (−1.35)	−0.38 (−0.15)	11.28 (1.80)	−15.66* (2.15)	−10.47 (−1.86)
Motor function	−1.41 (−0.82)	−1.46 (−0.66)	6.09 (0.89)	−9.57 (−1.16)	−5.44 (−0.86)
Attention	−0.27* (2.38)	−0.024 (−0.18)	0.49 (1.2)	−0.36 (−0.91)	−0.30 (−0.94)
Arithmetic	−4.67** (3.30)	−0.31 (−0.15)	11.46* (2.45)	−15.27** (2.95)	−11.50** (2.77)
Reading comprehension	−6.67*** (3.94)	1.62 (0.54)	19.64* (2.51)	−23.77** (2.68)	−18.93** (2.72)
Spelling	−2.06* (2.30)	0.022 (0.02)	4.53 (0.76)	−4.99 (−0.83)	−3.91 (−0.79)

that the thalamocortical system is affected by very preterm birth. Thalamocortical axons connect with the cortical plate neurons and become sensory-driven in terms of function between 29 and 32 weeks of postconceptional age (Kostović and Judaš, 2010), making this process vulnerable for disruptions by very preterm birth. Indeed, it has been shown that connections in the thalamocortical system are altered after very preterm birth (Ball et al., 2013), and that differences in structural (Ball et al., 2015) and fMRI (Toulmin et al., 2021) connectivity measures within the thalamocortical system are associated with cognitive outcome at 2 years of age in the very preterm born population. In addition, a recent multimodal neuroimaging sleep study showed that there might be a lasting misalignment between structural and functional thalamocortical connectivity in very preterm born children and adolescents as compared to term-born controls (Wehrle et al., 2020). However, exact neural mechanisms underlying the observed differences in beta PLI connectivity and beta PLI and AEC-c network measures between very preterm born adolescents and age-matched controls, and the relation between amplitude and phase coupling in general (Siems and Siegel, 2020), remain to be elucidated.

EEG is an important functional neuroimaging technique that can capture neurophysiological processes with high temporal resolution. Therefore, it is thought that functional EEG measures form a good representation of the functional capacity of the brain and are possibly closely linked to neurodevelopmental outcome. Our findings demonstrate that several EEG connectivity and network measures in the beta frequency band were indeed significantly associated with a variety of neurodevelopmental outcome measures after correction for very preterm birth. AEC-c connectivity was negatively associated with four out of six long-term outcomes, namely attention, arithmetic, reading comprehension and spelling. To our knowledge, there is no existing literature on associations between AEC-c connectivity and outcome measures in children or adolescents. Furthermore, LF was positively and maxBC and TH were negatively associated with arithmetic and reading comprehension in AEC-c based beta networks, taking into account the interrelatedness of network and connectivity measures in the parallel multiple mediator model. These findings indicate that less differentiated AEC-c based beta networks are associated with better functioning.

Very preterm born adolescents show significantly lower long-term outcome, despite the lower functional differentiation that was observed in this group. There were no mediation effects identified, indicating that lower outcome in very preterm born adolescents cannot be explained by the investigated functional brain activity measures. The lack of determinant-mediator interactions indicates that the relation between the investigated functional brain activity measures and outcome is similar in very preterm born adolescents and controls. Altogether, we identified differences in measures of functional brain activity between very preterm born adolescents and controls and we identified associations between functional brain activity and outcome measures. However, we were unable to reveal underlying brain mechanisms of impaired functioning in very preterm born adolescents.

The present study was limited by several factors. According to Fritz and MacKinnon, bias-corrected bootstrap mediations require a sample size of at least 116 subjects for a power of 0.8 when effects are medium (Fritz and Mackinnon, 2007). Ninety-six to 101 subjects were included for the final mediation analyses, and medium effect sizes for group comparisons were found (Fig. 3). Therefore, the present study was slightly underpowered, which should be considered during interpretation since it might fail to detect an existing effect. In addition, this was a single-center study, increasing the risk for lacking external validation. Furthermore, there was a bias in the present study group since adolescents without sufficient data quality had significantly lower neurodevelopmental outcome. The very preterm born study sample had less perinatal complications and better neurodevelopmental outcomes than adolescents who were lost to follow-up or had EEGs of insufficient quality. Consequently, the findings may underestimate alterations in brain function in the very preterm born population. The generalizability of the current study is limited by the sample characteristics: only Dutch adolescents, living in North-Holland, were included. Therefore, results might not be directly translatable to adolescents that were raised in other areas. Moreover, the data of the quantitative EEG analyses required a transformation to reduce the effect of outliers on the statistical analyses. These outliers may be related to medication use or the indication for medication use as described earlier (Albrecht et al., 2016). Though, sensitivity analyses for the group comparisons showed that exclusion of those that used methylphenidates or anti-epileptic drugs did not affect the results (data not shown).

5. Conclusions

Understanding mechanisms that cause adverse outcome after very preterm birth is necessary for the development of more effective intervention strategies to support very preterm born children. This study shows that very preterm born adolescents may have altered functional connectivity and brain network organization specific to the beta frequency band. Several AEC-c based connectivity and network measures were associated with neurodevelopmental functioning, indicating that quantitative EEG analysis is a promising tool for investigating mechanisms that underlie impaired functioning. However, alterations in measures of connectivity and network organization could not explain the differences in long-term outcome between very preterm and term born adolescents. At this stage, there are no direct clinical implications of the current findings. In the future, predictors of outcome should be available at an early age to facilitate early intervention strategies. Further work needs to be done to understand how alterations in brain activity contribute to impairments in functioning after very preterm birth to improve prognostication and support the development of new intervention strategies.

Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Funding

This study was partly supported by Danone Nutricia Research, Utrecht, the Netherlands. Danone Nutricia Research had no involvement in the conduct of the research.

Conflict of interest

None.

CRediT authorship contribution statement

C. Van't Westende: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Visualization. **E.S. Twilhaar:** Conceptualization, Methodology, Investigation, Writing – review & editing, Visualization, Supervision. **C.J. Stam:** Software, Conceptualization, Methodology, Writing – review & editing. **J.F. de Kieviet:** Conceptualization, Methodology, Writing – review & editing. **R.M. van Elburg:** Conceptualization, Methodology, Writing – review & editing. **J. Oosterlaan:** Conceptualization, Methodology, Writing – review & editing. **L.A. van de Pol:** Conceptualization, Methodology, Writing – review & editing, Supervision.

Appendix A. Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.clinph.2023.07.004.

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